Heart rate variability in electronic cigarette users

a randomized placebo-controlled crossover trial

Clothilde Claus

Promoteurs : Van de Borne Philippe (MD, PhD)

Co-promoteurs : Morra Sofia (MD) & Chaumont Martin (MD,PhD)

Hôpital Erasme

ULB

FARES

Variabilité de la fréquence cardiaque chez les utilisateurs de cigarette électronique

Un Essai croisé randomisé contrôlé par placebo

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FARES

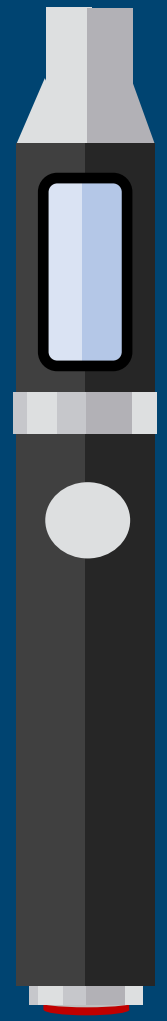
Variabilité de la fréquence cardiaque chez les utilisateurs de cigarette électronique

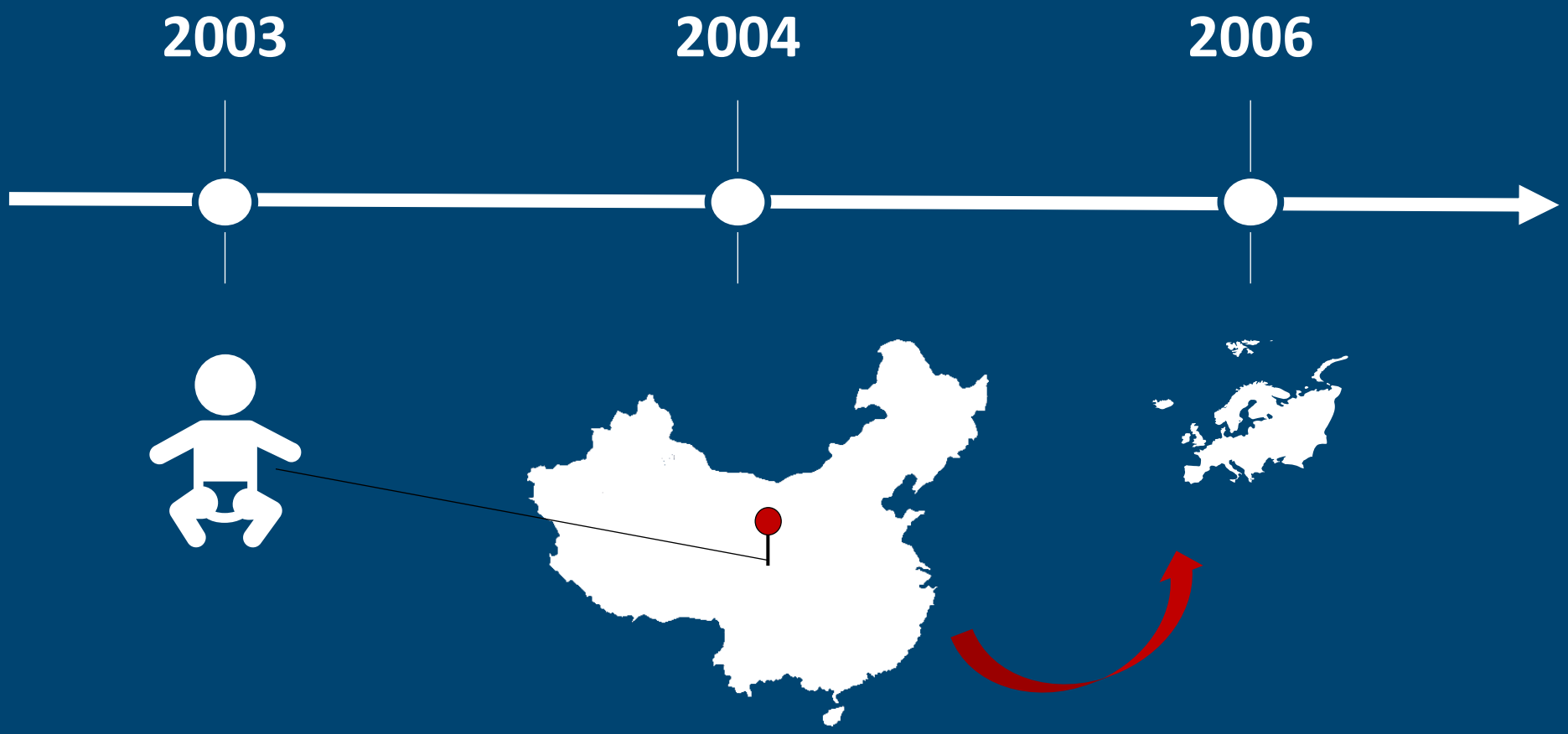
E-CIG?

HRV?

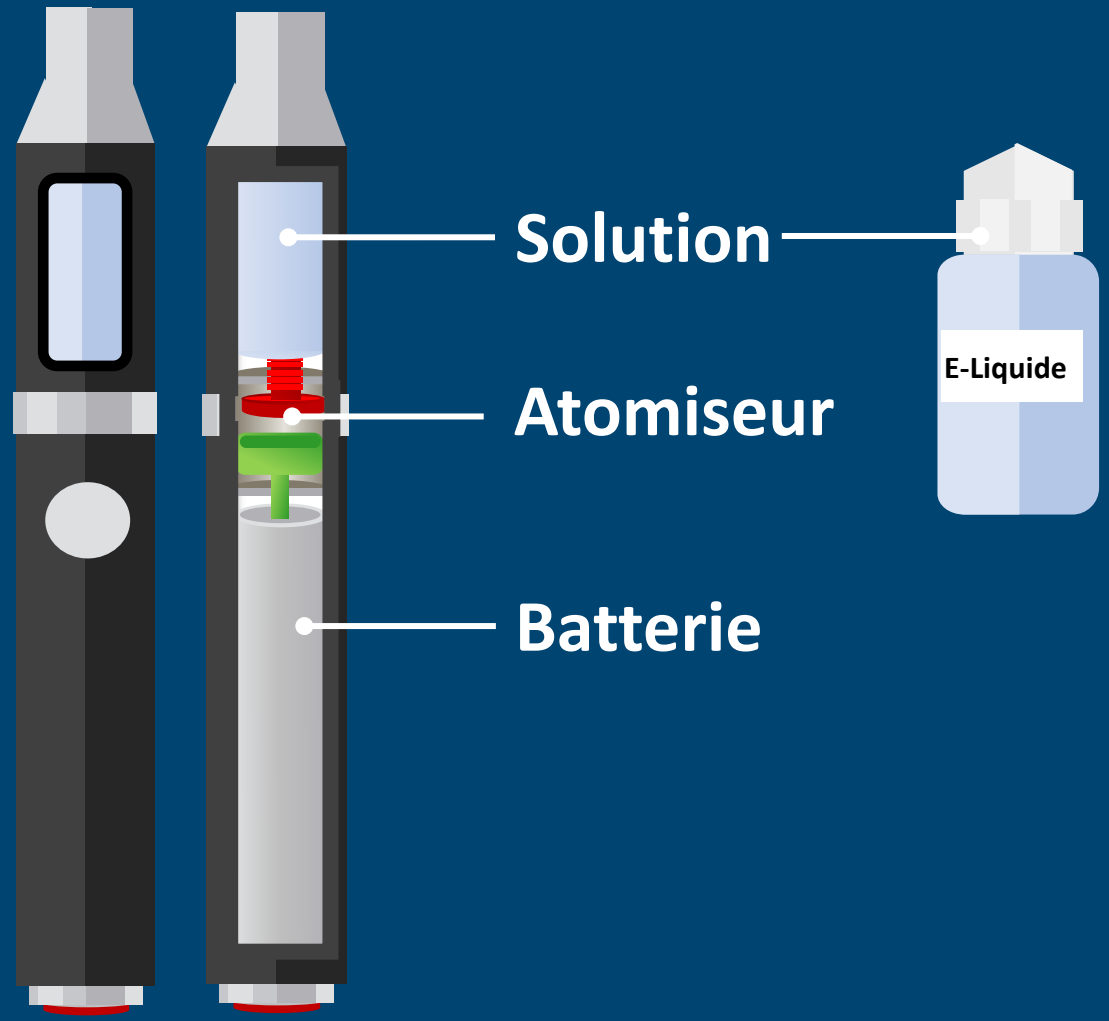
RÉSULTATS

CONCLUSION





Caponnetto P et al.2012



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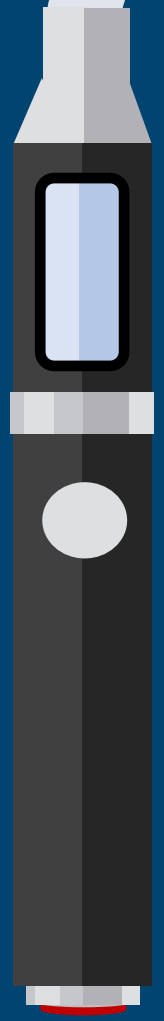
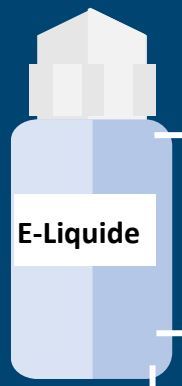




Arômes

> 7000 variétés sur la marché

Nicotine

Concentration Variable

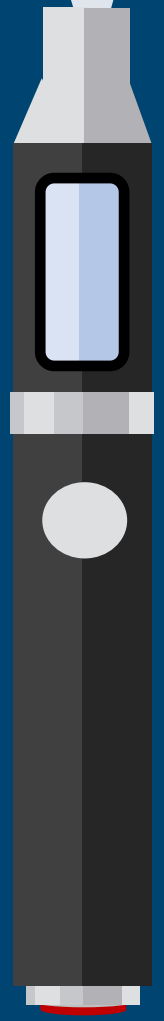
Solvant

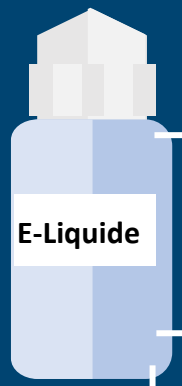
Propylène glycol (PG)

Glycérol (G)

FDA

Generally Recognized As Safe" compounds





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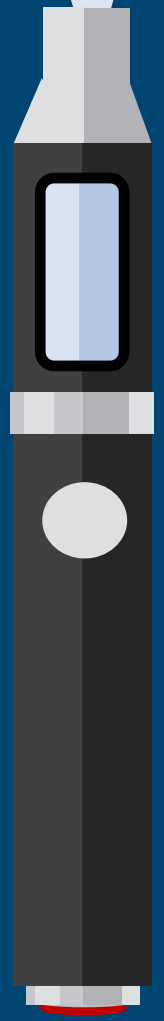
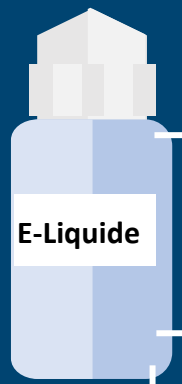
? ? ?





Arômes

Nicotine

Solvant

Propylène glycol (PG)

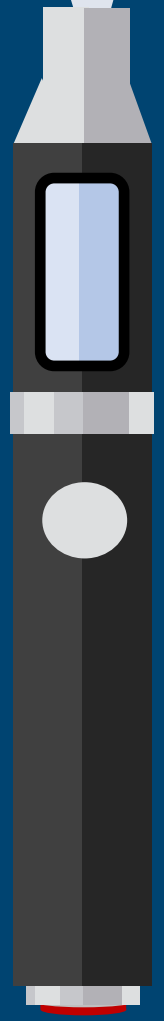
Glycérol (G)

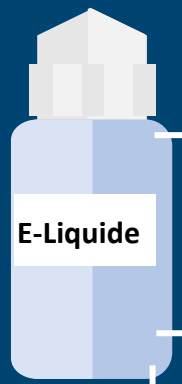
Diacétyl
Benzaldéhyde
Cinnamaldéhyde
Acétoine,…

Nicotine

Formaldéhyde
Propionaldéhyde
Acétaldéhyde
Acroléine,…

+ Autres toxiques





Arômes

Nicotine

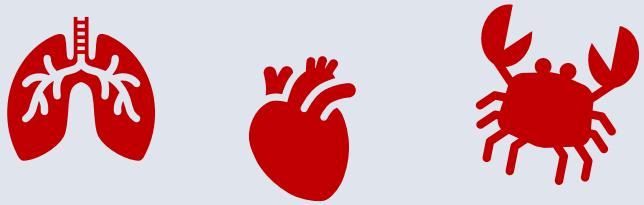
Delivery solvent

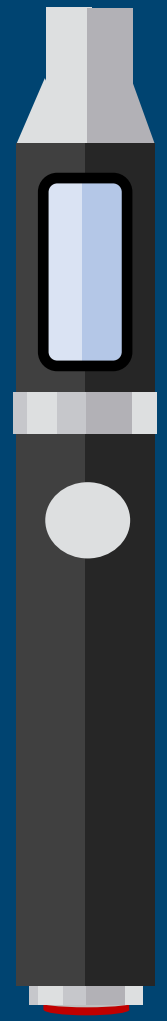
Propylène glycol (PG)

Glycérol (G)

Effets délétères connus

Contexte ≠ E-cig



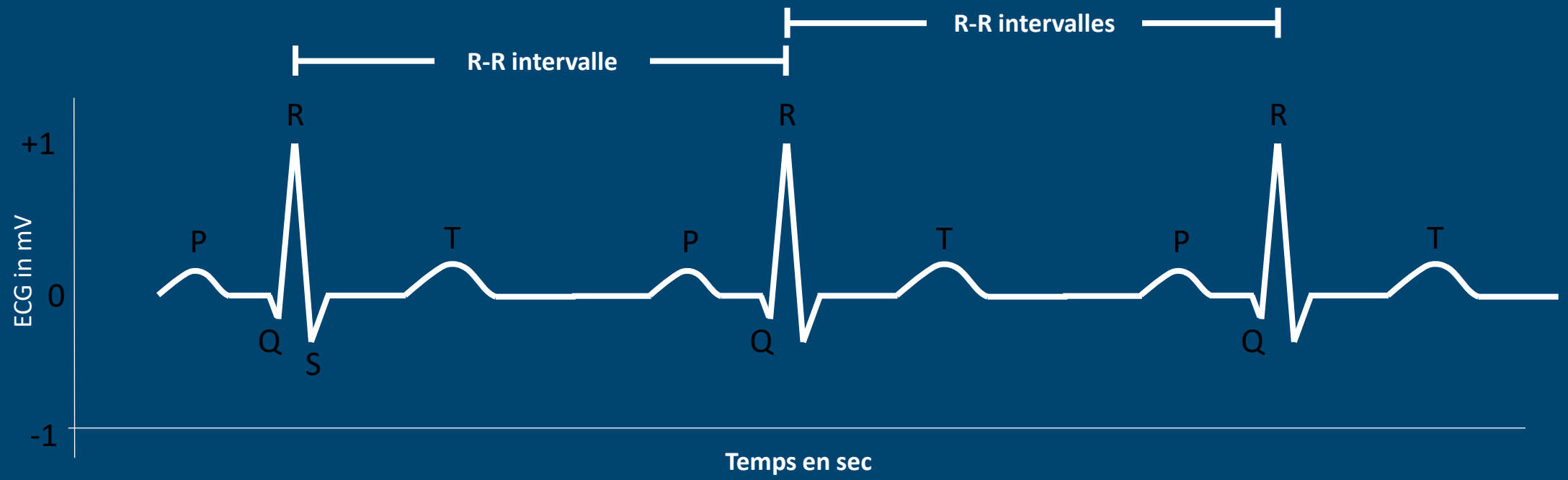


Effets délétères connus

Contexte ≠ E-cig

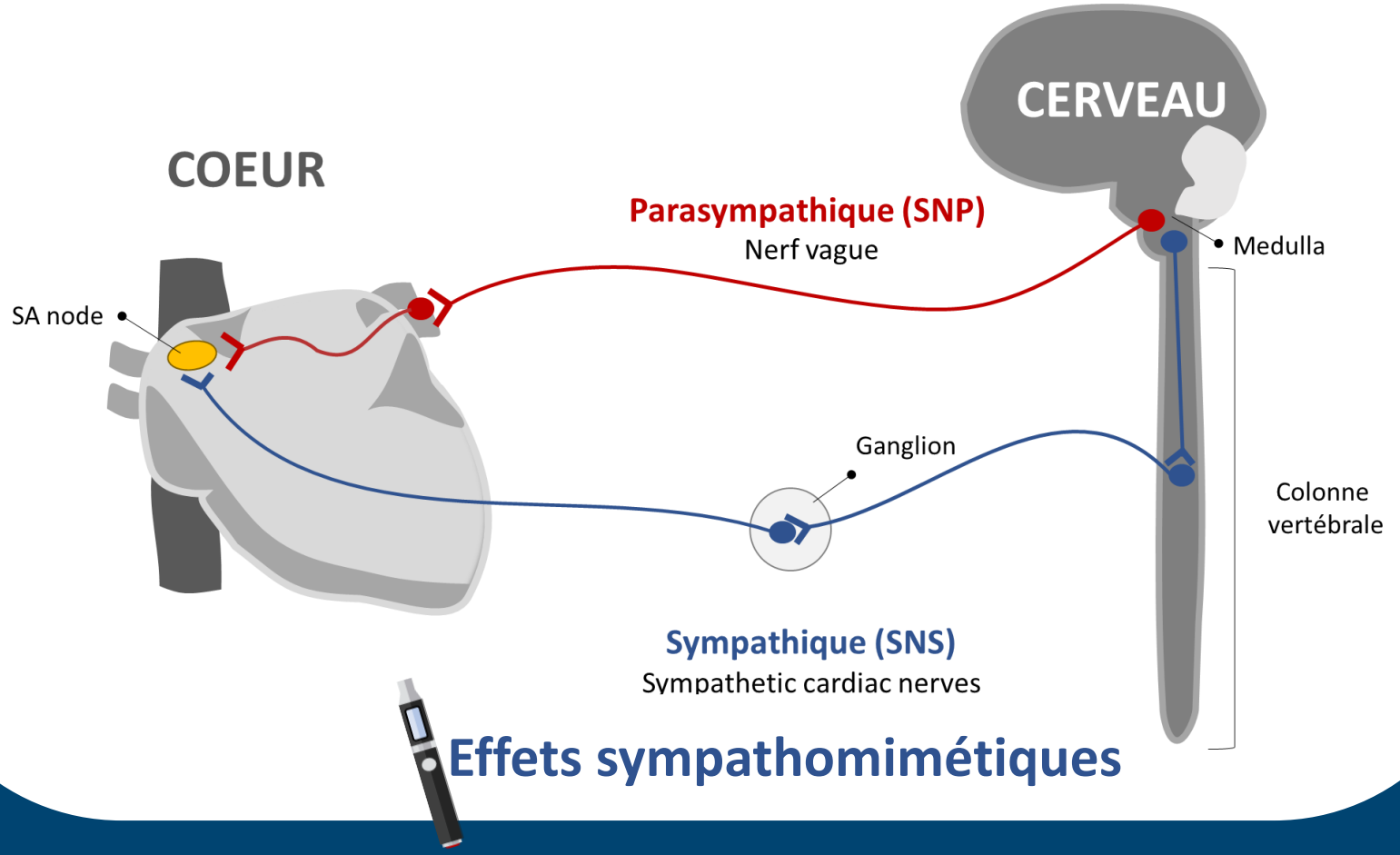
Effets courts et longs termes limités ?

HRV = Variabilité de la fréquence cardiaque



=Variation des intervalles de temps entre 2 battements

HRV = Variabilité de la fréquence cardiaque



Effets sympathomimétiques

+

Impact Vapotage aïgue / réversible

Am J Physiol Lung Cell Mol Physiol 318: L331–L344, 2020.
First published November 13, 2019; doi:10.1152/ajplung.00268.2019.

RESEARCH ARTICLE | *Electronic Cigarettes: Not All Good News?*

Short halt in vaping modifies cardiorespiratory parameters and urine metabolome: a randomized trial

Martin Chaumont,[1,2]* Vanessa Tagliatti,[3]* El Mehdi Channan,[1,2] Jean-Marie Colet,[3] Alfred Bernard,[4] Sofia Morra,[1,2] Guillaume Deprez,[5] Alain Van Muylem,[6] Nadia Debbas,[7] Thomas Schaefer,[8] Vitalie Faoro,[8] and Philippe van de Borne[1,2]

[1]Department of Cardiology, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium; [2]Institute for Translational Research in Cardiovascular and Respiratory Sciences, Université Libre de Bruxelles, Brussels, Belgium; [3]Department of Human Biology and Toxicology, University of Mons, Mons, Belgium; [4]Laboratory of Toxicology and Applied Pharmacology, Institute of Experimental and Clinical Research, Université Catholique de Louvain, Brussels, Belgium; [5]Department of Clinical Chemistry, Université Libre de Bruxelles, Brussels, Belgium; [6]Chest Department, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium; [7]Department of Cardiology, Centre Hospitalier Universitaire Saint-Pierre, Université Libre de Bruxelles, Brussels, Belgium; and [8]Cardio-Pulmonary Exercise Laboratory, Université Libre de Bruxelles, Brussels, Belgium

Submitted 5 July 2019; accepted in final form 5 November 2019

Chaumont M, Tagliatti V, Channan EM, Colet JM, Bernard A, Morra S, Deprez G, Van Muylem A, Debbas N, Schaefer T, Faoro V, van de Borne P. Short halt in vaping modifies cardiorespiratory parameters and urine metabolome: a randomized trial. *Am J Physiol Lung Cell Mol Physiol* 318: L331–L344, 2020. First published November 13, 2019; doi:10.1152/ajplung.00268.2019.—Propylene glycol and glycerol are e-cigarette constituents that facilitate liquid vaporization and nicotine transport. As these small hydrophilic molecules quickly cross the lung epithelium, we hypothesized that short-term cessation of vaping in regular users would completely clear aerosol deposit from the lungs and reverse vaping-induced cardiorespiratory toxicity. We aimed to assess the acute effects of vaping and their reversibility on biological/clinical cardiorespiratory parameters [serum/urine pneumoproteins, hemodynamic parameters, lung-function test and diffusing capacities, transcutaneous gas tensions (primary outcome), and skin microcirculatory blood flow]. Regular e-cigarette users were enrolled in this randomized, investigator-blinded, three-period crossover study. The periods consisted of nicotine-vaping (nicotine-session), nicotine-free vaping (nicotine-free-session), and complete cessation of vaping (stop-session), all maintained for 5 days before the session began. Multiparametric metabolomic analyses were used to verify subjects' protocol compliance. Biological/clinical cardiorespiratory parameters were assessed at the beginning of each session (baseline) and after acute vaping exposure. Compared with the nicotine- and nicotine-free-sessions, a specific metabolomic signature characterized the stop-session. Baseline serum club cell protein-16 was higher during the stop-session than the other sessions ($P < 0.01$), and heart rate was higher in the nicotine-session ($P < 0.001$). Compared with acute sham-vaping in the stop-session, acute nicotine-vaping (nicotine-session) and acute nicotine-free vaping (nicotine-free-session) slightly decreased skin oxygen tension ($P < 0.05$). In regular e-cigarette-users, short-term vaping cessation seemed to shift baseline urine metabolome and increased serum club cell protein-16 concentration, suggesting a decrease in lung inflammation. Additionally, acute vaping with and without nicotine decreased slightly transcutaneous oxygen tension, likely as a result of lung gas exchanges disturbances.

electronic nicotine delivery systems; metabolomics; nicotine; pneumoproteins; transcutaneous oxygen tension

INTRODUCTION

Propylene glycol and glycerol, the main constituents of electronic-cigarette (e-cigarette) liquid (e-liquid), produce an aerosol when heated that carries flavoring and nicotine. High-wattage vaping, which enhances heat and aerosol production, is the modality of choice for regular users (vapers) (10–12, 57). High-wattage vaping, with and without nicotine, has been shown to induce transcutaneous hypoxia, constriction of the airways, and lung inflammation in healthy naïve vapers (10, 12). The latter was marked by a rise in serum club cell secretory protein-16 (CC16) without a change in surfactant protein-D (10–12). Acute nicotine-free-vaping decreased partial pressure of arterial oxygen (O_2) and the oxyhemoglobin fraction in heavy tobacco smokers (naïve vapers), suggesting lung gas exchange disturbances (12).

Propylene glycol and glycerol are small hydrophilic molecules that swiftly cross the lung epithelium (19, 21, 42). When vaped in large amounts, however, this aerosol can transiently accumulate deep in the lungs (42) and interact with the epithelium (50). This hygroscopic and hyperosmolar deposit could theoretically disrupt the rheological properties of surfactant and mucus (21, 23, 31, 49, 50, 52), resulting in bronchiolar and alveolar collapse and therefore impairments to lung gas exchange (40). This possibility is supported by in vitro and animal studies (26, 42, 43, 58, 59), but it is not known if it also occurs in humans (44). We hypothesized that short-term cessation of vaping in regular heavy e-cigarette-users would completely clear aerosol deposit from the lungs, with subsequent recovery of gas exchange and restoration of biological/clinical cardiorespiratory parameters. We also explored whether e-cigarette cessation for 5 days could shift serum and urine

* M. Chaumont and V. Tagliatti contributed equally to this work.
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  ISSN 1040-0605.

Effets sympathomimétiques

+

Impact Vapotage aïgue / réversible

Vapoteurs Réguliers

- ≥ 1 an E-cig
- Bonne santé
- ~~Traitement médicamenteux~~
- ~~Drogue récréative~~

Effets sympathomimétiques

+

Impact Vapotage aïgue / réversible

Vapoteurs Réguliers

3 Sessions Étudiées

3 Sessions Étudiées

5 jours

Exposition aïgue

Nicotine session

Vapotage régulier +nicotine

Paramètres de Base

Paramètres Post-Exp.

+ nicotine

7 j

Nicotine free-session

Vapotage régulier sans nicotine

Paramètres de Base

Paramètres Post-Exp.

PG/G sans nicotine

7 j

Stop-session

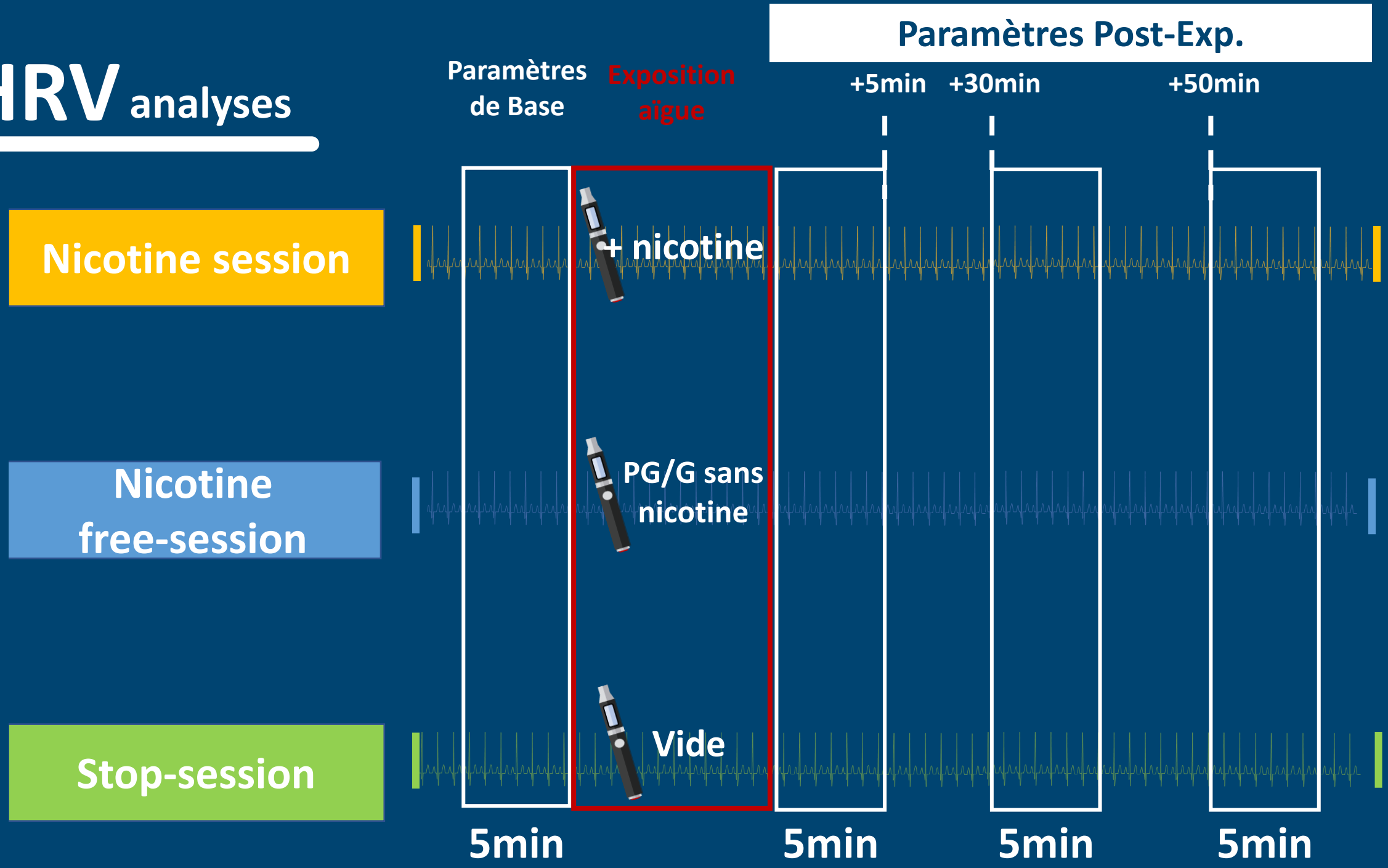
Aucun vapotage

Paramètres de Base

Paramètres Post-Exp.

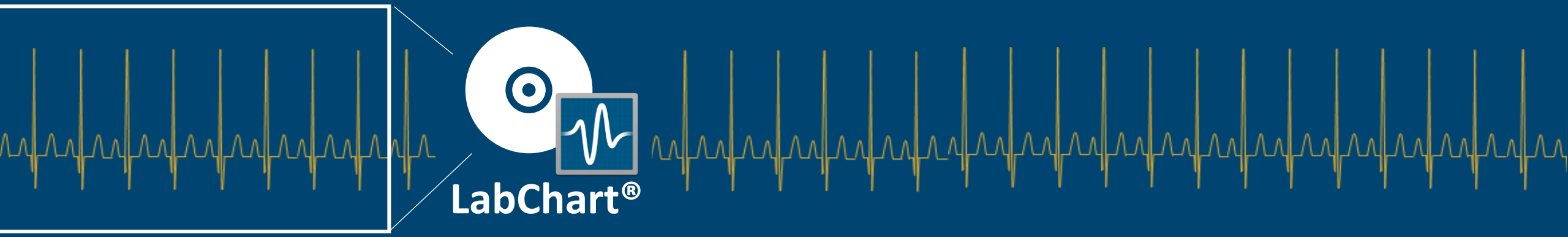
Vide

HRV analyses



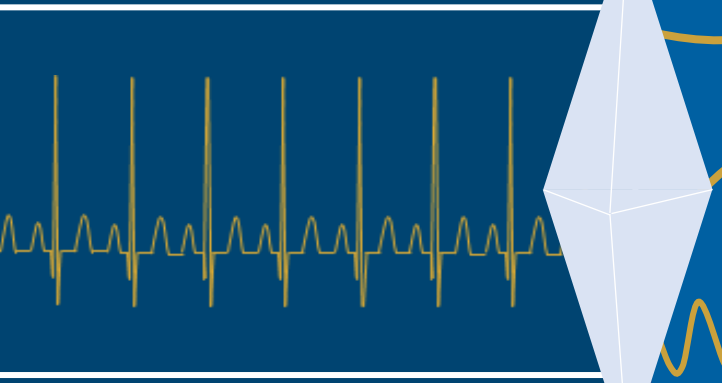
HRV analyses

5min



HRV analyses

5min



Analyse spectrale

Oscillation lente

Oscillation rapide

Sympathique

Base fréquence (LF) 0,04Hz – 0,15Hz

ParaSympatique

Haute fréquente (HF) > 0,15Hz-0,5Hz

Domaine temporel

Domaine Fréquentiel

https://www.academie-medecine.fr/wp-content/uploads/2014/02/pages-175-186.pdf

OBJECTIFS

- Effets **ARRÊT COURT** vapotage avec/sans nicotine sur HRV chez utilisateurs réguliers de e-cig

- Effets **utilisation aïgue du** vapotage avec/sans nicotine sur HRV chez utilisateurs réguliers de e-cig.

Résultats

Méthode: domaine fréquentiel

- Étude des Baselines
- Étude des Baselines vs paramètres post-exposition
- Étude HRV/session

n=30, test Bonferroni’s correction

Résultats

Méthode: domaine fréquentiel

- Étude des Baselines

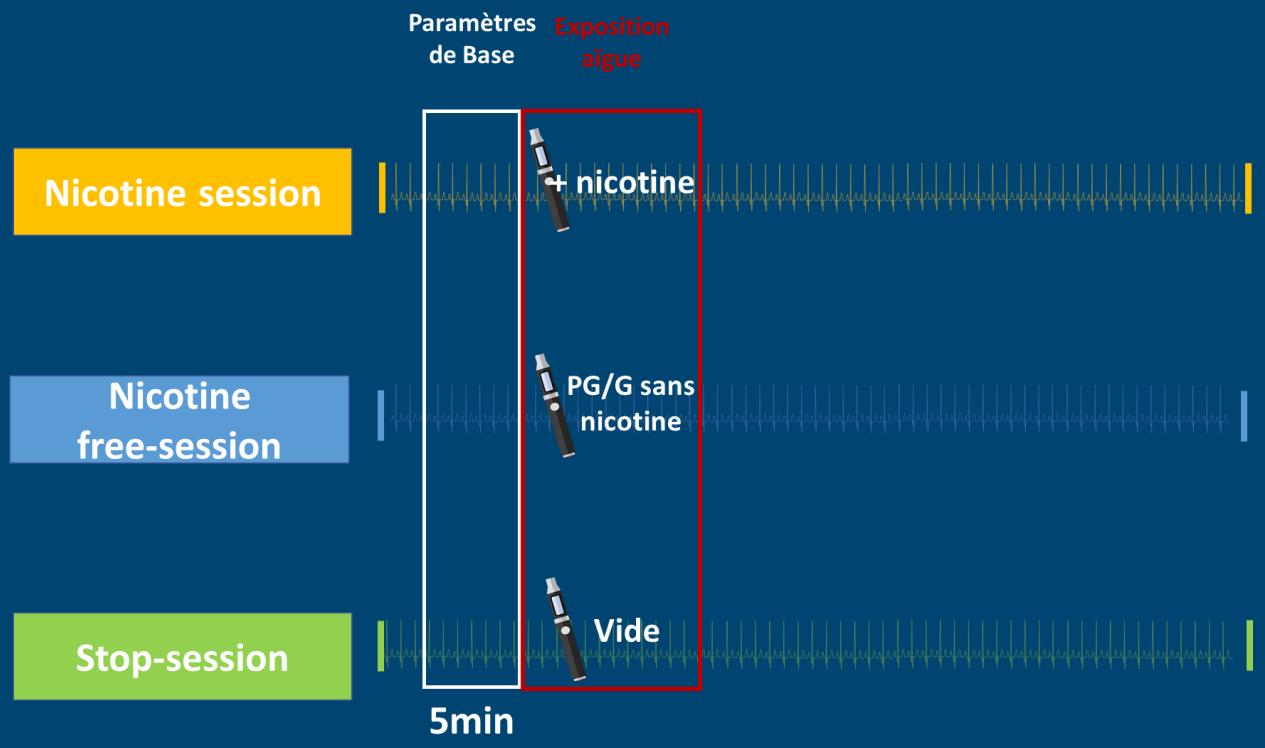


Table 1 –Comparison of HRV baseline parameters between sessions						
HRV parameters	Nicotine session[A]	Nicotine-free session[B]	Stop session[C]	p^{AvsB}	p^{AvsC}	p^{BvsC}
HR (bpm)	67.3 ± 1.7	64.2 ± 1.8	64.1 ± 1.6	0.053	***0.004***	0.32
Total Power (ms^2)	6800 [4929-18953]	8617 [5487-15675]	5533 [3468-14720]	0.07	0.09	0.92
LF Power (nu)	51.7 ± 4.3	52.7 ± 4.3	58.0 ± 4.4	0.81	0.23	0.37
HF Power (nu)	44.7 ± 3.6	44.6 ± 3.8	40.2 ± 4.0	0.91	0.34	0.34
LF/HF (nu)	1.1 [0.8-2.2]	0.9 [0.6-2.9]	1.4 [0.9-3.1]	0.82	0.46	0.34
HRV, heart rate variability; HR, heart rate; LF, low frequency; HF, high frequency; LF/HF ratio. Data are presented as mean ± SD or median [P25-P75] according to data distribution.						

Arrêt à court terme
→ Pas d'impact sur la HRV
→ Impact sur la fréquence cardiaque (HR)

n=30, test Bonferroni's correction

Résultats

Méthode: domaine fréquentiel

- Étude des Baselines vs **paramètres post-exposition**

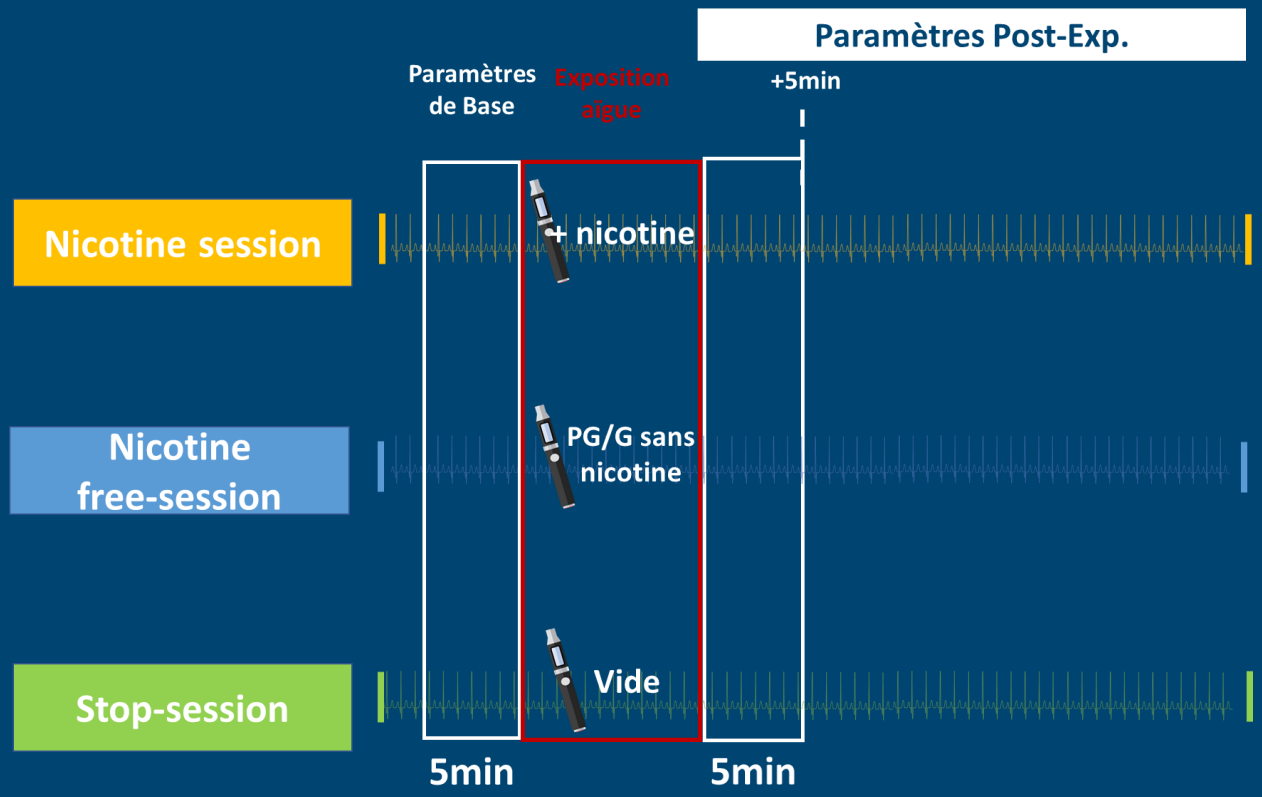


Table 3 – Comparison of the difference (Δ) of acute vaping values with BSL values between sessions.

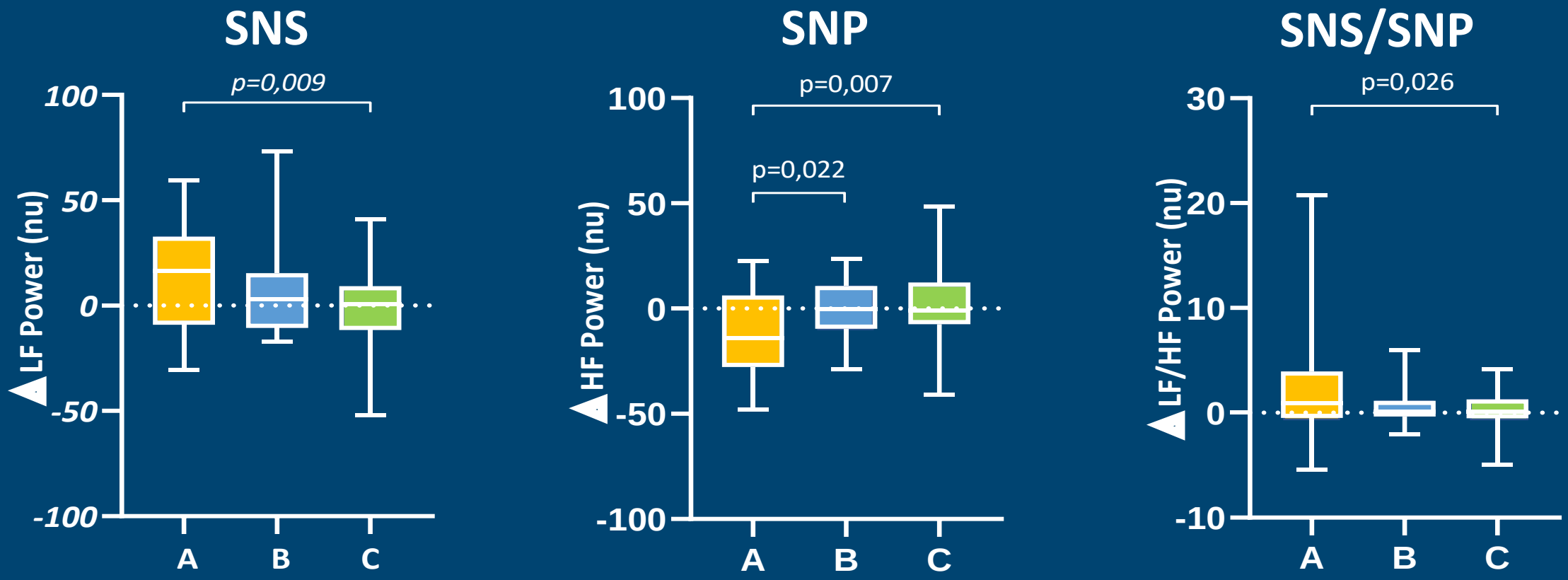
HRV parameters	Nicotine session[A]	Nicotine-free session[B]	Stop session[C]	p^{AvsB}	p^{AvsC}	p^{BvsC}
ΔHR (bpm)	5.8 [2.9; 13.5]	- 0.6 [-1.9; 1.5]	0.3 [-1.3; 2.1]	***0.041***	***0.002***	0.9
ΔTotal Power (ms^2)	-3517 [-11669 ; 403]	-1224 [-4403 ; 1435]	-207 [-2744 ; 2273]	0.29	0.19	0.16
ΔLF Power (nu)	16.3 [-9.1 ; 32.8]	3.1 [-10.6 ; 15.4]	0.8 [-11.7 ; 9.2]	0.18	***0.009***	0.13
ΔHF Power (nu)	-13.9 [-27.7 ; 6.3]	-0.14 [-9.6 ; 10.8]	-0.8 [-7.4 ; 12.4]	***0.022***	***0.007***	0.39
ΔLF/HF (nu)	0.9 [-0.5 ; 3.9]	0.07 [-0.37 ; 1.15]	0.1 [-0.5 ; 1.3]	0.09	***0.026***	0.12

HRV, heart rate variability; HR, heart rate; LF, low frequency; HF, high frequency; LF/HF ratio. Data are presented as median [P25-P75] according to data distribution.

n=30, test Bonferroni’s correction

Résultats

Méthode: frequency-domain



Nicotine session

Nicotine free-session

Stop session

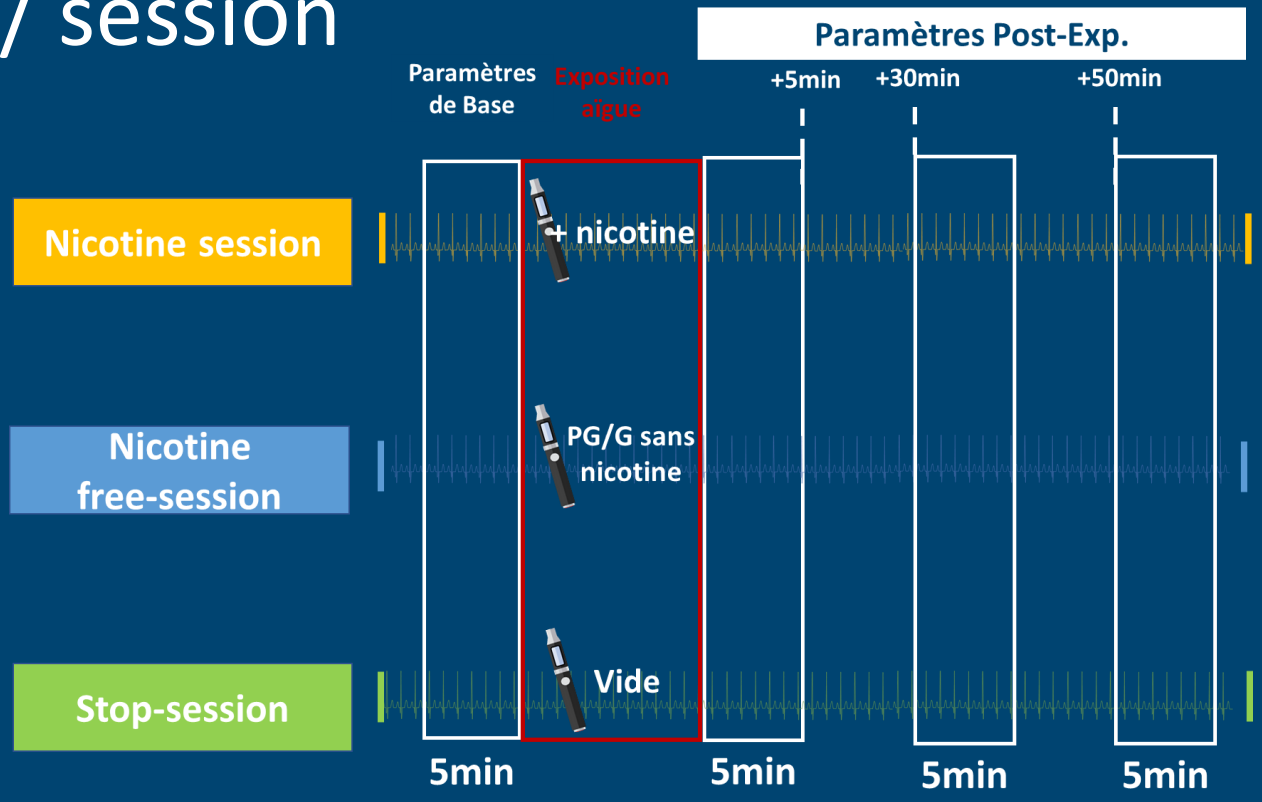
L'exposition aiguë à la nicotine ↑ l'activité du SNS

n=30, test Bonferroni's correction

Résultats

Méthode: domaine fréquentiel

- Étude HRV/ session

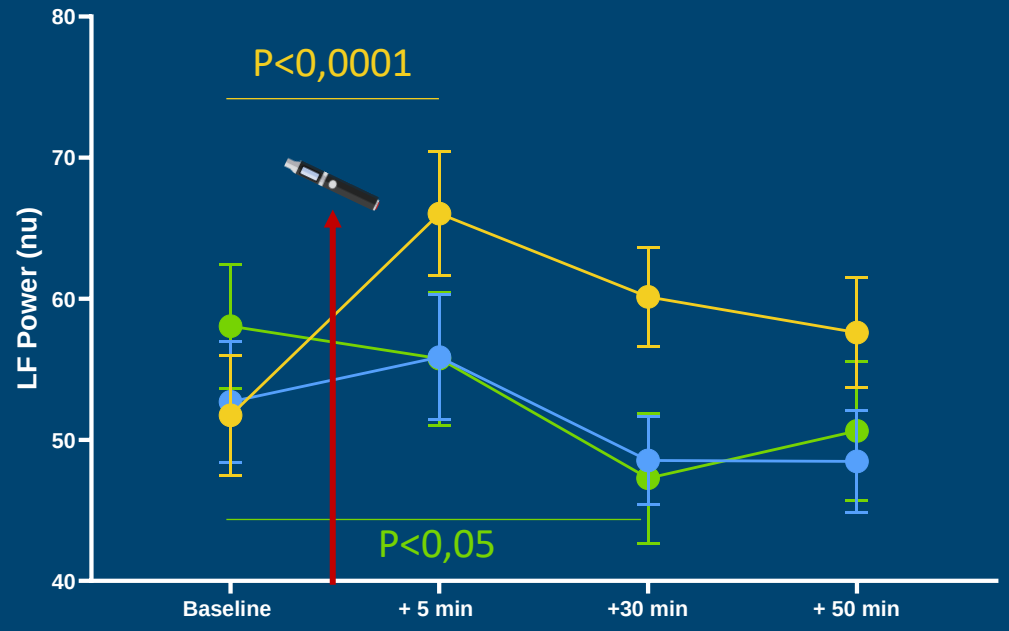


n=30, test Bonferroni's correction

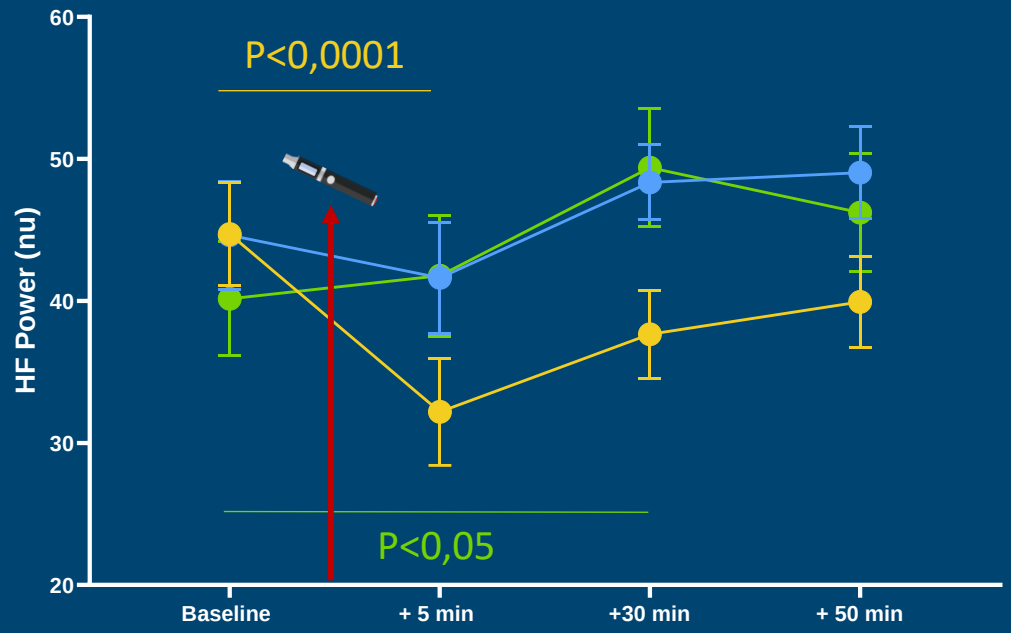
Résultats Principaux

Méthode: frequency-domain

Sympathique



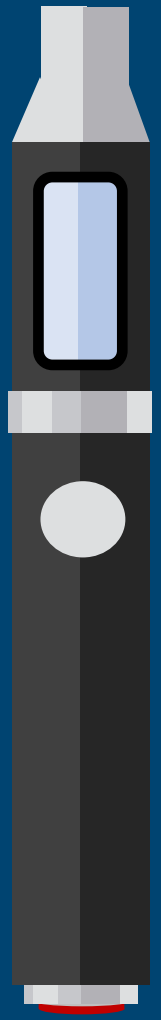
Parasympathique



Nicotine session
Nicotine free-session
Stop session

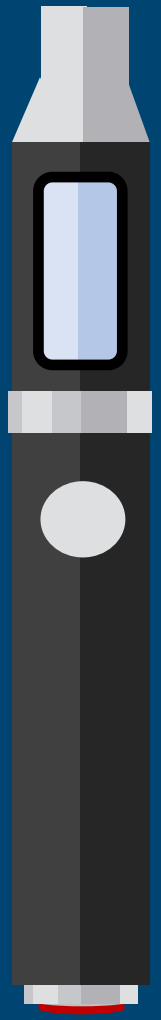
n=30, test Bonferroni's correction

Conclusions & Perspectives



- L’exposition aiguë à la nicotine ↑ l’activité du SNS.
- Prédominance SNS < Nicotine et non des autres composants.
- Arrêt à court terme pas d’impact sur le HRV.

Conclusions & Perspectives



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- Arrêt à court terme pas d’impact sur le HRV.

Impact de l’arrêt à long terme /réversibilité de l’effet de la E-cig et sa prédominance sur le SNS ?

Références

Dia 3	Image from -https://www.spreadshirt.com/shop/design/hon+lik+vape+godfather+vaping+e-juice+new+hot+mens+t-shirt-D5d89f4942051762642236033?sellable=JkpXG977pYIZGm1Yxw1g-210-7Caponnetto Caponnetto P et al., Expert Rev Respir Med. 2012; 6(1):63-74
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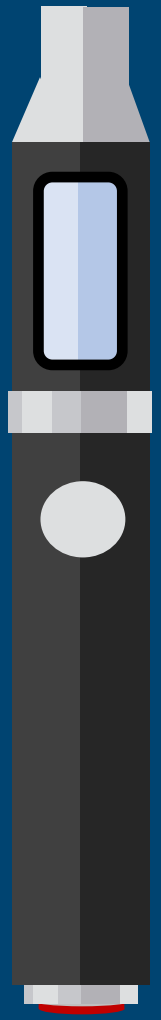
Dia 13	Chaumont et al., Am J Physiol Lung Cell Mol Physiol. 2020; 318(2): L331–L344.
Dia 15-16	Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Eur Heart J. 1996;17(3):354-81. Järvelin-Pasanen et al., Ind Health. 2018; 56(6): 500–511; Shaffer F et al. Front Public Health. 2017; 5: 258
Dia 17	Moheimani et al., J Am Heart Assoc 2017; 6:e006579; Moheimani et al., JAMA Cardiol. 2017 ;2(3):278-284; Arastoo et al., Am J Physiol Heart Circ Physiol. 2020 Aug 1;319(2):H262-H270.

Hôpital Erasme ULB

CSFT 2020

FARES



Merci pour votre attention.

Clothilde@claus.live

Annexes

Exposition aïgue _ E-cig utilisée

A fourth-generation e-cigarette set at 60 W (Ailen 220 box mod, TFV8 baby beast tank and a dual Kanthal coil (V8 Baby-Q2 Core; 0.40 dual coils); Smoke, Shenzen, China) with MXJO (Mojotech, Shenzen, China) mAh 35A variable voltage/variable wattage batteries.

Nicotine session	**NICOTINE** at a concentration of 1.5 mg/mL + **GLYCOL/GLYCEROL** was mixed by the pharmacy at Erasme University Hospital (50/50 vol/vol; pharmaceutical grade; Fagron, Waregem, Belgium)
Nicotine free-session	**NICOTINE** + **GLYCOL/GLYCEROL** was mixed by the pharmacy at Erasme University Hospital (50/50 vol/vol; pharmaceutical grade; Fagron, Waregem, Belgium)
Stop-session	Sham-vaping was identical to active vaping but with the e-cigarette turned off

75 sessions étudiées

Essai croisé (“cross-over”)

- Patient = son propre témoin

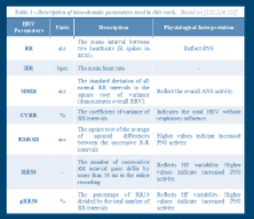
Successivement traitement étudié + traitement contrôle → Ordre aléatoire

Méthode Time-domain/ domaine temporel

- Méthode + ancienne
- Déterminer la fréquence cardiaque à tout instant t

→ **USE: étude HRV long terme**

Expl: Variables dérivées directement de la mesure des intervalles R-R:



HRV Parameters	Units	Description	Physiological Interpretation
RR	ms	The mean interval between two heartbeats (R spikes in ECG).	Reflect PNS
HR	bpm	The mean heart rate.	-
SDNN	ms	The standard deviation of all normal RR intervals is the square root of variance (demonstrates overall HRV).	Reflect the overall ANS activity
CVRR	%	The coefficient of variance of RR intervals.	Indicates the total HRV without respiratory influence.
RMSSD	ms	The square root of the average of squared differences between the successive R-R intervals	Higher values indicate increased PNS activity
NN50	-	The number of consecutive RR interval pairs differ by more than 50 ms in the entire recording	Reflects HF variability. Higher values indicate increased PNS activity
pNN50	%	The percentage of NN50 divided by the total number of RR intervals	Reflects HF variability. Higher values indicate increased PNS activity

Méthode frequency-domain/ domaine fréquentiel

- Méthode mathématique permettant de déceler les différentes oscillations d'un rythme

→ **USE: étude HRV court terme**

4 composantes spectrales

- Hautes fréquences (HF)
- Basses fréquences (LF)
- Très basses fréquences (VLF)
- Ultra basses fréquences (ULF)

HRV Parameters	Units	Description	Physiological Interpretation
Total Power	ms²	Total variance corresponding to the sum of the four spectral bands (ULF, VLF, LF and HF)	Reflects overall ANS activity
LF Power	ms²	Low-frequency power (frequency band 0.04–0.15 Hz)	-
LF Power	%	Percentage of LF power, representing the relative power in proportion to the total power. LF power/Total power × 100	Higher: ↑ SNS activity
LF Power	nu	LF power in normalized units (nu), representing the relative power in proportion to the total power minus the VLF component. LF power/(Total power − VLF power)	
HF Power	ms²	High-frequency power (frequency range 0.15–0.4 Hz)	-
HF Power	%	Percentage of HF power, expressed the relative power in proportion to the total power. HF power/Total power × 100	Higher: ↑ PNS activity
HF Power	nu	HF power in normalized units (nu), expressed the relative power in proportion to the total power minus the power of the VLF component. HF power/(Total power − VLF power)	
LF/HF	ms	Ratio of LF to HF relative power in normal units	Shifts of balance SNS and PNS activity

Transformation de Fourrier

La transformation de Fourier $\mathcal{F}$ est une opération qui transforme une fonction intégrable sur $\mathbb{R}$ en une autre fonction, décrivant le spectre fréquentiel de cette dernière. Si f est une fonction intégrable sur $\mathbb{R}$, sa transformée de Fourier est la fonction $\mathcal{F}(f) = \hat{f}$ donnée par la formule :

$$\mathcal{F}(f) : \xi \mapsto \hat{f}(\xi) = \int_{-\infty}^{+\infty} f(x)\, e^{-i\xi} \, \mathrm{d}x.$$

Variabilité de la fréquence cardiaque (HRV)

Fluctuation du rythme cardiaque au cours du temps entre deux battements consécutifs, et dépend essentiellement de la régulation extrinsèque de la fréquence cardiaque.

- Reflet de l'activité du SNA
- Méthode non invasive / reproductible
- Biomarqueur pour le diagnostic et le suivi évolutif de multiples pathologies chez l'homme
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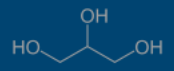
+ Stress

Dépendance (Tumeur activité SNS↑ , nouveaux né exposé à forte de dose de nicotine)

Glycérol - Propylène Glycol



- Liquide incolore
- Visqueux
- Inodore
- Goût sucré,
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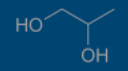

- Utilisé à faible dose comme additif alimentaire

Exposition aïgue _ E-cig utilisée

Réf: https://www.cdiscount.com/au-quotidien/articles-fumeur/smok-220w-alien-kit-avec-2x-vtc5-batterie-tfv8-bab/f-12712-dan0713830101853.html

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Nicotine free-session

~~**NICOTINE**~~
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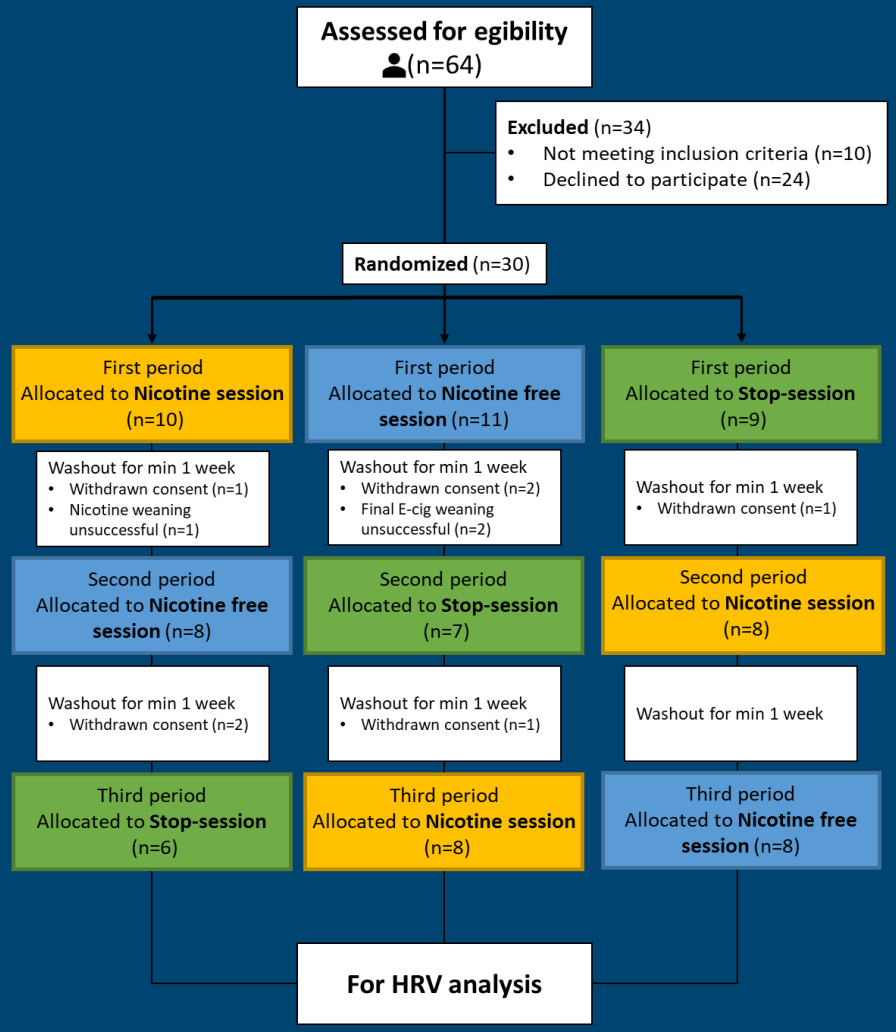
Sham-vaping was identical to active vaping but with the e-cigarette turned off

Réf: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7052663/

75 sessions étudiées



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- Patient = son propre témoin

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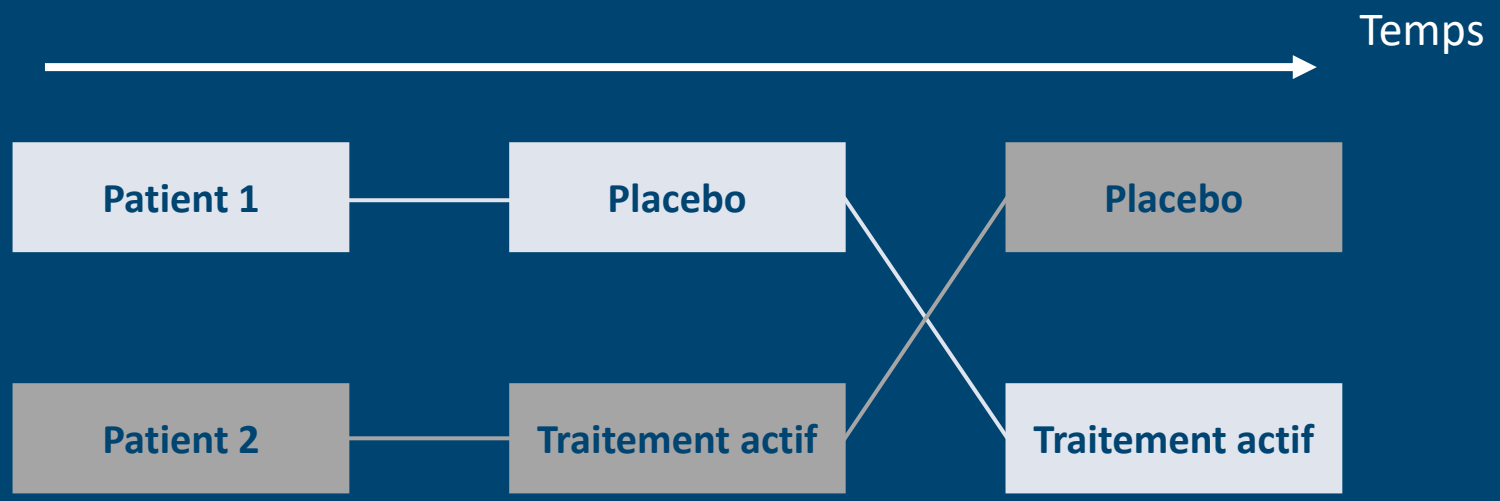

- > Essai en bras // à effectif identique
- 2 fois moins de patients nécessaires
- Diminue la variabilité (chaque patient est son propre témoin)

- Nécessite que l’état des patients soit similaire en début des 2 périodes Maladies chroniques Médicaments non curatifs
- 2 fois plus long (2 périodes de traitement + wash-out)
- Risque d’arrêt prématuré, de sortie d’essai, de perdus de vue
- Effet « carry over » (intérêt du wash-out)
- Effet période (apprentissage)

Réf: http://www.txrating.org/spc/polycop/cross%20over.htm, https://websaraf.net/IMG/pdf/bases_methodologiques.pdf

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RR50	-	The number of consecutive RR interval pairs differ by more than 50 ms in the entire recording	Reflects HF variability Higher values indicate increased PNS activity.
pRR50	%	The percentage of RR50 divided by the total number of RR intervals	Reflects HF variability. Higher values indicate increased PNS activity.

Järvelin-Pasanen S, et al. 2018; Park D et al. 2018; Mietus JE 2002

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Table 1 – Description of frequency-domain parameters used in this work. Based on [122].

HRV Parameters	Units	Description	Physiological Interpretation
Total Power	ms^2	Total variance corresponding to the sum of the four spectral bands, LF, HF, ULF and VLF.	Reflects overall ANS activity.
LF Power	ms^2	Low-frequency power (frequency range 0.04–0.15 Hz)	Marker of SNS activity.
LF Power	%	Percentage of LF power, representing the relative power in proportion to the total power: LF power/Total power × 100.	
LF Power	nu	LF power in normalized units (n.u.), representing the relative power in proportion to the total power minus the power of the VLF component: LF power/ (Total power – VLF power).	
HF Power	ms^2	High-frequency power (frequency range 0.15–0.4 Hz) (synchronous with respiration)	Marker of PNS activity.
HF Power	%	Percentage of HF power represent the relative power in proportion to the total power, HF power/Total power ×100%	
HF Power	nu	HF power in normalized units (n.u.) represent the relative power in proportion to the total power minus the power of the VLF component, HF power/ (Total power – VLF power)	
LF/HF	nu	Ratio of LF-to-HF relative power in normal units	Marker of global SNS and PNS balance.

Järvelin-Pasanen S et al.2018

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La transformation de Fourier $\mathcal{F}$ est une opération qui transforme une fonction intégrable sur $\mathbb{R}$ en une autre fonction, décrivant le spectre fréquentiel de cette dernière. Si f est une fonction intégrable sur $\mathbb{R}$, sa transformée de Fourier est la fonction $\mathcal{F}(f) = \hat{f}$ donnée par la formule :

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https://fr.wikipedia.org/wiki/Transformation_de_Fourier

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Réf: https://www.academie-medecine.fr/wp-content/uploads/2014/02/pages-175-186.pdf

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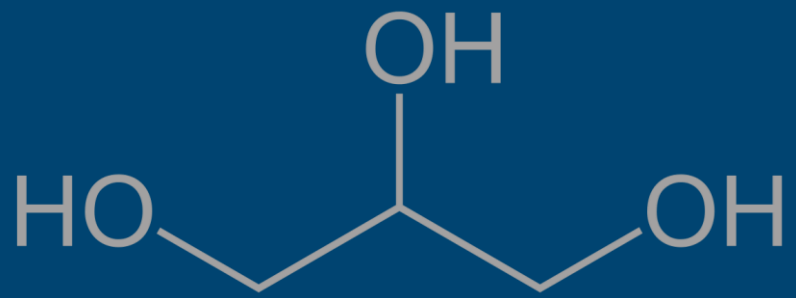

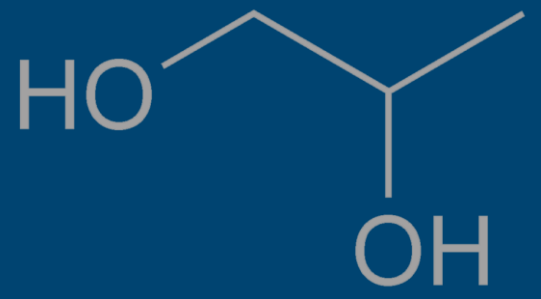

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https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/glycerol_fr.pdf

Bonferroni-Holm

Utilisée pour contrer le problème des comparaisons multiples .

Elle est destinée à contrôler le taux d'erreur par famille et offre un test simple uniformément plus puissant que la correction de Bonferroni .

Il porte le nom de Sture Holm , qui a codifié la méthode, et de Carlo Emilio Bonferroni .

https://en.wikipedia.org/wiki/Holm%E2%80%93Bonferroni_method#Motivation